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METHOD AND DEVICE FOR GLUCOSE CONCENTRATION MEASUREMENT WITH SPECIAL ATTENTION TO BLOOD GLUCOSE DETERMINATIONS

BACKGROUND OF THE INVENTION

5   The invention relates to techniques for non-invasive
measuring of blood glucose concentration, especially in
diabetics.

       It is well known that glucose in solution is an optically
active material. That is, it will cause the plane of
polarization of light traversing the solution to be rotated. The
10 quantitative relationship between the amount of polarization
rotation, the glucose concentration, and the optical path length
of the solution has been clearly established. It is known that
this phenomenon offers the potential for developing a non-
invasive blood glucose analyzer.

15   Diabetes is a disease which entails a large number of
associated complications. Retinal deterioration leading to
blindness and impaired circulation leading to limb amputation are

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just two of the more serious complications. Many of these
complications result from the large excursions in blood glucose
concentrations common to diabetics due to inadequate monitoring
of the blood glucose levels. Current methods of diabetic
monitoring of blood glucose involve the lancing or sticking of a
finger and external measurement of the glucose content of the
blood sample. This procedure leaves the diabetic with sore
fingers, since the recommended frequency of testing is four or
more times per day.

Although many diabetes patients should use the "finger
sticking" test to obtain blood for glucose concentration
measurements four or more times per day, studies show that very
few patients do this unless they absolutely have to, and many
patients only do it a few times at the beginning of their
treatment until they establish what they think is a pattern in
their required medication schedule. They then stop the finger
sticking tests and simply take their insulin shots on the
assumption that their body chemistry is thereafter constant.
This leads to large changes in glucose concentration in the
patient's blood, which in turn leads to a variety of serious
medical consequences to the patient. For example, it is
estimated that in 1996 there were over fifty thousand amputations
of limbs due to complications of diabetes in the U. S.

Diabetics recover from cuts and bruises more slowly than do

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non-diabetics. This very real and basic discomfort causes many diabetics to shirk on the frequency of blood glucose testing, resulting in a higher frequency of complications than otherwise would be the case. A small device that could make blood glucose

5   measurements on a non-invasive basis would be of great value to the diabetic in that it would greatly encourage frequent monitoring of blood glucose levels.

Glucose in solution is an example of an optically active substance. That is, the glucose solution will rotate the plane

10   of polarization of polarized light passing through it in proportion to the path length in the solution and to the concentration of the glucose in the solution. This is expressed mathematically as:

Eq. 1 $\Delta\theta = \alpha * L * C$

15   Where:

$\Delta\theta$ is the polarization rotation in degrees;

α is the specific rotation constant dependent on the specifics of the glucose type;

α = 56.5 (35.4) degrees per decimeter (dm) per gram per

20   milliliter for sucrose at a wavelength of 633 (780) nanometers

L   is the path length in the solution in dm, (where 1 dm = 10 centimeters (cm);

C   is the glucose solution concentration in grams (gm) per milliliter.

5   For the clinically meaningful glucose concentration range from 50 to 500 mg/dL (milligrams per deciliter) and a path length of 1 cm, the observed rotation ranges from about 0.0028 degrees to about 0.028 degrees for a wavelength of 633 nanometers. As the wavelength is increased the specific rotation α decreases, to

10   a value of 26.3 at a wavelength of 900 nanometers. At that wavelength the rotation in the above case is reduced to 0.0013 and 0.013 degrees respectively. If the assumption is made that about 30% of the path length of radiation passing through living tissue is comprised of blood while the remainder is made up of

15   fat, bone, sinew, etc. then a 1 cm path length through human tissue should produce about 0.001 to 0.01 degrees of polarization rotation. Thus, a useable system must have a basic sensitivity of the order of about 0.0003 degrees, i.e., 1 arc-second, or 5 micro radians.

20   It is known that human tissue is basically transparent in the wavelength range from about 750 nanometers to about 1800 nanometers. This is the spectral region known as the "overtone" region. It lies between the electronic, or atomic transition, wavelength region on the short wavelength side and the molecular

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vibrational-absorption region on the long wavelength side. Since
there are no fundamental absorption processes in this region, it
is found that organic materials basically have quite reasonable
optical transmission in this region of the spectrum.

5   Patent 5,209,231 by Cote et al. describes a non-invasive
glucose sensor which utilizes a pair of polarizers, a quarter
wave plate and a motor driven polarizer which produces a constant
amplitude phase modulated beam. This beam is split into two
beams, one of which passes through the sample and the other which
10   is employed as a reference. By phase demodulation of the two
beams, each incident on a different detector, a measure of
glucose concentration in an optical cell is determined.
Measurements are proposed to be made transversely through the
eye's anterior chamber (e.g., 53 in Fig. 7). This approach
15   suffers in sensitivity of measurement (according to the authors)
which is probably due to noise problems associated with the motor
driven phase modulator as well as other unidentified problems.

"Multispectral Polarimetric Glucose Detection using a Single
Pockels Cell", Optical Engineering, Vol. 33, pp 2746 (1994) by
20   King et al. describes a system which employs a pair of
polarizers, a quarter wave plate, and a Pockels cell modulator
which are configured as a polarization spectrometer. They
employed the output from a lock in amplifier which is "filtered
using a leaky integrator" and then fed back to a compensator

circuit which was eventually summed with the driver oscillator output and then input to the Pockels cell driver to null the AC signal in the system. Again, noise levels in the system represent the major problem in achieving the required sensitivity. The reported data show a scatter that is unacceptable for a working blood glucose sensor.

The angle of incidence of the input beam to the cornea and the exit angle therefrom as shown in Fig. 1 of the King et al. article are so large that the instrumentation, including small turning mirrors or the like, must be positioned very close to the patient's sclera or the soft tissue near the base of his/her nose and the soft tissue at the outer corner of the eye that it is difficult to provide the input beam and to intercept the exit beam, especially with a portable instrument. Furthermore, these angles are sufficiently large that it is difficult to "initialize" the apparatus by rotating the polarizer and analyzer sufficiently to produce the initial extinction of the beam required. The angles required of a prism which would provide the same angle of incidence and exit angle for initial alignment of the apparatus are so large that a suitable prism is very expensive. While the size and shape of the human eye does not vary substantially from person to person, the soft tissue structure surrounding the eye does vary greatly from person to person. This makes it difficult to design support structures for the turning mirrors required to provide the incidence beam and

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intercept the exit beam.

"Noninvasive Glucose Monitoring of the Aqueous Humor of the
Eye: Part I. Measurement of Very Small Optical Rotations",
Diabetes Care, Vol. 5, pg 254, by Rabinovitch et al. describes a
system having two polarizers, and two Faraday rotator/modulators.
In this case there was no quarter wave plate employed in the
apparatus. The absence of the waveplate means that their system
is vulnerable to ellipticities of polarization which might be
produced by mirror or optical surface reflections as well as any
problems with scattering by the sample or any surfaces in the
optical beam. According to the authors, noise in the system "was
sufficiently large to make reading the fourth decimal difficult".
Thus a sensitivity of less than one part in 10,000 was achieved.
Since it is readily observed that a sensitivity of one part in
100,000 represents the minimally acceptable sensitivity in a
practical measurement system, this approach is also unacceptable.

Patents 5,398,681 and 5,448,992 by Kupperschmidt refer to
the phase-sensitive measurement of blood glucose and both patents
employ (different) systems having a sample and a reference beam
which are phase modulated relative to each other. It remains to
be demonstrated whether or not successful measurements can be
obtained with the Kupperschmidt apparatus.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the invention to provide a device capable of measuring the concentration of an optically active ingredient in a sample.

It is another object of the invention to provide a device capable of measuring an optically sensitive ingredient in biological tissue in a non-invasive manner.

It is another object of the invention to provide an improved apparatus and method for obtaining a null value in making a polarization rotation measurement.

It is another object of the invention to provide an apparatus and method for determining the concentration of an optically active ingredient in the anterior chamber of the eye which avoids inaccuracies due to variation in the optical path length of a beam through the anterior chamber of the eye.

It is another object of the invention to avoid the problems in initializing a measurement apparatus prior to making a glucose concentration measurement based polarization rotation of a beam in the anterior chamber of an eye.

It is another object of the invention to provide an

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apparatus and technique to introduce an optical beam into the anterior chamber of the eye and receive the transmitted beam without touching the sclera of the eye or soft tissue around the eye.

5   It is another object of the invention to provide a device capable of measuring the sucrose concentration of human blood in a non-invasive manner.

        It is another object of this invention to provide a new very sensitive and stable polarization spectrometer which has
10   applications in ellipsometry and in certain types of chemical analysis.

        Briefly described, and in accordance with one embodiment thereof, the invention provides a system and method for measuring the concentration of an optically active substance, for example
15   glucose, in the anterior chamber of an eye, by guiding a beam, preferably of collimated monochromatic light, through a polarizer oriented in a first direction to polarize the light in a first direction, and then through a polarization modulator and an analyzer oriented in the second direction to polarize the light
20   in a second direction; the beam is guided from the analyzer to a detector, and at least one of the polarizer and the analyzer is adjusted to extinguish light of the beam to prevent it from passing from the analyzer to the detector; after the beam passes

through the polarizer, the beam is guided so that it is generally parallel to an iris of the eye as it is introduced into the anterior chamber wherein it is refracted, impinges on the iris, is reflected therefrom, and then exits the anterior chamber approximately collinear with the beam immediately before the point at which it is introduced into the anterior chamber. The beam exiting from the anterior chamber is guided onto the detector. A signal is applied to the polarization modulator just sufficient to extinguish light passing from the analyzer to the detector. The DC signal then represents the concentration of the glucose in the anterior chamber. The beam preferably also is passed through a quarter wave plate after it exits from the polarizer. In one embodiment the orientation of a portion of the beam incident on a cornea of the eye is adjusted until a stable, substantially increased output signal level is produced by the detector. In that embodiment and also in a different embodiment the polarization modulator can be a Faraday rotator, wherein a DC signal and an AC signal are applied to a coil of the Faraday rotator to extinguish light of the beam to prevent it from passing from the analyzer to the detector by shifting the DC signal to a value that produces a null in the AC component of a corresponding output signal produced by the detector. The value of the shifted DC signal then represents the glucose concentration in the anterior chamber. The output signal of the detector is applied to an input of a lock-in amplifier, and the null has been achieved when a DC output of the lock-in amplifier

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is zero. In the described embodiments the DC signal is a DC current having a value in the range of about 0.01 to 100 milliamperes, and the AC signal is an AC current having a range in the value of about 0.01 to 10 amperes, to thereby greatly

5 reduce noise in the detector output, to the range of a few millivolts or less.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a diagram illustrating a conventional polarization spectrometer.

Fig. 2 is a diagram illustrating a blood glucose polarization spectrometer according to the present invention.

Fig 3 is a diagram useful in explaining the offset difference method of polarization rotation determination used in the embodiment of Fig. 2.

Fig. 4 is a diagram illustrating lock-in amplifier output signal in accordance with the method of Fig. 3.

Fig. 5 is a block diagram of the blood glucose analyzer system used in conjunction with the embodiment of Fig. 2.

Fig. 5A is a circuit schematic drawing of the current source 31 and filter 33 of Fig. 5.

Fig. 5B is a circuit schematic drawing of the signal conditioning in circuit 38 of Fig. 5.

Fig. 5C is a circuit schematic drawing of the chopper circuitry 42 of Fig. 5.

Fig. 5D is a circuit schematic drawing of the photodiode 47 and detector and preamplifier circuitry 48 of Fig. 5.

Fig. 6 is a graph indicating the detector output signal versus sucrose concentration.

Fig. 7 is a cross sectional view of a human eye useful in describing the invention.

Fig. 8A is a diagram showing an alternative optical path useful for blood glucose determinations by using the anterior chamber of the eye.

Fig. 8B is a frontal view of the alternative optical path of Fig. 8A.

Fig. 8C is a graph illustrating the detector output signal when the embodiments of the invention according to Figs. 8A and 8B are utilized.

Fig. 9A is a diagram of an apparatus employing turning mirrors to guide a beam to and from the eye as the measurement site.

Fig. 9B is a diagram of an apparatus employing a pair of optical fiber collimators to guide the beam to and from the eye

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as the measurement site.

Fig. 10 is a graph indicating in vivo measurements of blood glucose concentrations in several individuals using transmission through the anterior chamber of the eye.

5   Fig. 11 is a diagram illustrating a hand held embodiment for measurement of glucose concentration in the anterior chamber of the eye.

Fig. 12 is a diagram illustrating another hand held embodiment for measurement of glucose concentration in the
10   anterior chamber of the eye.

Fig. 13 is a diagram illustrating a hand held embodiment for measurement through the skin of an individual.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

To assemble a small device capable of making rapid and accurate determinations of glucose concentrations under such conditions, it is advantageous to utilize several newly developed components including optical fibers, high Verdet constant glass optical phase modulators, and small, dedicated microprocessors. (A glass with a high Verdet constant is one that has a relatively large amount of polarization rotation under the application of a given magnetic field.)

In one embodiment of the proposed device, light from an LED or laser diode is collimated and polarized. This parallel light beam is passed through a quarter wave plate and subsequently a section of an electro-optic material such as PLZT which acts as a polarization modulator via optically active phase modulation. (Alternatively, a section of high Verdet constant glass can be placed inside a small helical coil of copper wire and, by passing current through the coil, a longitudinal magnetic field is created which acts on the glass to rotate the plane of polarization of the light passing through it. This phenomenon is known as the Faraday effect and the device is known as a Faraday rotator.) The light can be routed to the glucose sample at the selected measurement site by mirrors or by a fiber optic collimator.

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The light is collected by a second mirror or optical fiber collimator and is routed through the analyzer, which is rotated so as to obtain total extinction of the light beam. Finally the light is routed to a focusing lens and a silicon detector. The DC voltage applied to the phase modulator or the DC current through the Faraday rotator is adjusted to compensate exactly for the glucose solution rotation, and this DC voltage or current then provides the measure of the phase rotation caused by the glucose in the sample, and hence the glucose concentration therein.

In accordance with the present invention, detector sensitivity is enhanced by the application of a large AC modulation voltage/current superimposed onto the small DC voltage applied to the phase modulator or the DC current applied to the Faraday rotator. Known lock-in amplifier techniques, subsequently described, are employed to optimize the sensitivity or detectivity of the overall system.

One major complicating factor involved in this methodology, for the case that measurement takes place through skin and tissue, lies in the depolarization of the transmitted beam due to scattering of the beam by the non-homogeneous media (bone, sinew, blood platelets, etc.) of the human body. This scattering results in an overall ellipticity of the transmitted beam and a resultant decrease in the precision in the measurement. By

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introducing a quarter wave plate into the optical system, it is possible to compensate for this depolarization effect and restore the sensitivity of the measuring apparatus. Small errors that may be introduced by misalignment of the components or by small

5   strains in the various elements of the system can be compensated for by means of a pre-measurement calibration procedure and appropriate orientation of the polarizer, analyzer and quarter wave plate.

For the case that the measurement takes place through the

10 anterior chamber of the eye this problem does not exist since the cornea of the eye provides a transparent window into an optically clear sample fluid (the aqueous humor). This is important, because there have been several clinical studies that confirm a direct relationship between a patient's blood-glucose

15 concentrations and glucose concentrations in the aqueous humor of the anterior chamber of the patient's eye.

The proposed optical blood glucose analyzer is based on a modified polarization spectrometer. The components of a basic spectrometer, shown in Fig. 1, include a laser diode or light

20 emitting diode 2 which is a monochromatic light source, the output of which is collimated by a collimating lens 3 and transmitted to a polarizer 4. Arrows 5 indicate the direction of polarization of light passing through polarizer 4. The resulting polarized light passes through a quarter wave plate 6. Feature

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23 of quarter wave plate 6 represents the capability of a quarter

wave plate to modify the relative phases of polarized light beams

to produce elliptically or even circularly polarized light.

Quarter wave plate 6 is followed by an analyzer 7, in which

5   arrows 8 represent the direction of polarization of analyzer 7.

The light emanating from analyzer 7 passes through focusing lens

9 and is focused onto a suitable detector, such as a silicon

photodiode, which produces an output signal 11 that represents

the amount of light that is transmitted through the entire

10   spectrometer. For a very carefully oriented polarizer, quarter

wave plate, and analyzer system the transmission is about 1 part

in 100,000 of the light incident on the first polarizer.

Basic polarization spectrometer 1 is capable of analyzing

any combination of linearly and elliptically polarized light.

15   Its precision is limited only by the quality of the polarizers 4

and 7 and the capability of determining the "position" of the

intensity minimum at the detector.

Polarizers having extinction ratios of several tens of

thousands are now readily available. The extinction ratio is

20   defined as the light intensity transmitted by two parallel

oriented polarizers to that transmitted by two perpendicularly

oriented polarizers. The precision with which the extinction

position of polarizer 4 and analyzer 7 can be measured directly

is about 0.3-0.5 degrees due to the gradual change of

transmission about the extinction point. For "crossed"
polarizers 4 and 7 (placed at 90 degrees relative to each other),
the transmission as a function of $\Delta\theta$ is given by

Eq. 2 $\qquad I + I_o \sin^2(\Delta\theta),$

5   which is a slowly varying function about the extinction position
($\Delta\theta = 0$). This precision is clearly not satisfactory for the
problem at hand.

By alternately rotating analyzer 7 about its null position
by plus and minus a few degrees, it is possible to determine
10   positions of equal intensity on each side of the null position
and then use the average value of these two readings as the true
null position. In this method, the precision is limited by the
ability to read divided circles accurately as well as by the
precision of the divided circles themselves. The inventor has
15   demonstrated a precision of about plus or minus 0.01 degrees when
this method is employed. This precision thus approaches the
required value of 0.0003 degrees (or 1 arc second or about 5
micro radians), but remains somewhat short of the desired
accuracy.

20   An additional component referred to as a "modulator/rotator"
can be used to measure the rotation of polarization in a totally
electronic manner, as opposed to the conventional method of

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physically rotating polarizer 4 and analyzer 7 to effect the
measurement.

Fig. 2 shows the additional components required with those
in Fig. 1 for the determination of blood glucose at satisfactory
accuracy levels, including a modulator/rotator 20 and a suitable
tissue sample 22. There are several devices that can serve as
the modulator/rotator. The Faraday effect rotator, described
above is one such device. A second device would be a solid state
Kerr cell. A Kerr cell is a system in which the electric field
is applied transversely to the propagating light beam. The
medium of the Kerr cell can range from liquids, such as
nitrobenzene, to crystalline materials, such as KDP (potassium
di-hydrogen sulfate) or amorphous solids, such as PLZT (lead
lanthanum zirconate-titanate). Another candidate device would be
a Pockels cell, in which the electric field is applied along the
propagation direction in an appropriate crystalline medium, such
as again KDP. Arrows 21A and 21B shown in modulator/rotator 20
are simply a diagrammatic symbol to indicate that the plane of
polarization is changed by the modulator.

To measure the blood glucose or blood glucose level in
tissue sample 22, the apparatus 1A of Fig. 2 is aligned
optically, and the quarter wave plate fast axis is manually
aligned at 45 degrees to the axis of polarizer 4. (In a quarter
wave plate, there are two mutually perpendicular directions or

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"axes" which lie in the plane of the plate. They are the "fast"

and the "slow" axes and correspond to the velocities of the two

characteristic polarized waves in the crystal.) Then alternately

analyzer 7 and polarizer 4 are successively adjusted until output

5   signal 11 indicates that total extinction is achieved (with no

sample present) and with zero activation of modulator/rotator 20.

Then the sample 22 is introduced, and modulator/rotator 20

is activated so as to again produce extinction in the transmitted

beam. The amount of DC voltage/current applied to

10   modulator/rotator 20 to achieve this extinction is then a measure

of the glucose concentration.

A series of calibration measurements employing known glucose

concentrations in water uniquely establish the relationship

between the DC activation voltage/current and the glucose

15   concentrations. The diagram of Fig. 6 shows this relationship.

In the embodiment of Fig. 2 the DC voltage or current

activation component applied to the optical phase

modulator/rotator 20 has an AC component superimposed on it of

sufficient amplitude to cause plus and minus rotation of some few

20   degrees. Then the determination can be made as follows:

The DC component is adjusted so as to produce a precisely

equal plus and minus amplitude swing in the AC component. This

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manual offset movement method has been shown to provide a measurement capability in $\Delta\theta$ of some plus or minus 0.01 degrees when the analyzer position is determined by the reading of a divided circle (this manual approach does not involve any type of

5 modulator/rotator). Such precision, although greatly improved over the pure extinction method, remains inadequate for useful blood glucose determinations. By the use of the electronic phase modulator/rotator and the employment of phase sensitive detection methods a still greater precision of approximately 0.0001 degrees

10 (0.35 arc second or 1.5 micro radians) has been experimentally demonstrated. This sensitivity will provide a precision in blood glucose concentrations of better than 2 mg/dL, which value will permit the determination to be made to better than 5% of even the lowest meaningful concentrations.

15 The method of determining the precise null position is illustrated in Fig. 3, wherein the main curves A and B represent the $\sin^2(\Delta\theta)$ dependence of detector output signal 11 as a function of polarization rotation. Curve A in Fig. 3 shows the output for a DC activation which is offset from true null and the

20 consequent anisotropic output of the detector. Curve B in Fig. 3 shows the situation for an exact null position.

Fig. 4 shows the output which would derive from a lock-in amplifier being employed in the detector circuit.

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I have found that the accuracy of determining the exact DC
null position is dependent on how precisely the lock-in zero of
the detector output can be located. I also have found that an
accuracy of 0.01 millivolts (mv) is observed, while the signal of
5   rotation (for 100 mg/dL glucose concentration) is 1.12 mv; thus a
precision of about 1% or about 1 mg/dL has been realized with
this methodology.

The method of coupling both an AC and a DC voltage or
current component to an optical modulator/rotator so as to avoid
10   the inaccuracies due to various noise sources is described below
with reference to Fig. 5. In the measurement configuration, two
superimposed signals are applied to the coil of the Faraday
rotator 20. An AC sine wave current signal having a frequency of
about 475 hertz applied to the coils of the Faraday rotator
15   causes the polarization of the Faraday rotator 20, and hence the
detector output signal, to alternately shift to either side of
the optical null. A constant DC current also is applied to the
coil so as to center the AC fluctuations equally to either side
of optical null.

20   In the experimental embodiments which I have constructed and
tested to date, the DC signal is a DC current having a value in
the range of about 0.01 to 100 milliamperes, and the AC signal is
an AC current having a value in the range of about 0.01 to 10
amperes in order to reduce the noise in the detector output

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signal on conductor 11 to the range of a few millivolts or less.
In miniaturized future devices having redesigned Faraday
rotators, the above values will be different. What is probably
most important is that the ratio between the AC and DC currents

5   will be from about 10,000 to 1,000,000. This range of ratios of
the AC voltage to the DC voltage magnitudes probably will be also
applicable if the Faraday rotator is replaced by a Kerr cell or a
Pockels cell.

      The initial value of the DC current applied to the coil of

10   the Faraday rotator 20 is selected to produce the needed magnetic
field through which the laser beam passes. For example, a DC
current of approximately 0.1 milliamperes through the coil of the
Faraday rotator 20 might produced a desired "bias value" of the
magnetic field therein. For the apparatus which I have

15   constructed and tested, an AC modulation voltage of 15 volts
peak-to-peak, to thereby produce a 1 ampere peak-to-peak AC
modulation current in the Faraday rotator coil having a
resistance somewhat less than 15 ohms, was found necessary to
achieve the desired sensitivity and accuracy of the DC balance

20   point voltage as shown in curve B of Fig. 3. The $\sin^2$ nature of
the polarization modulator or Faraday rotator 20 is that with the
foregoing value of AC modulation, the noise present, being
superimposed on the detector output signal, has sufficiently
negligible effect on the DC balance point shown for curve B in

25   Fig. 3 that the DC balance point current very accurately

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represents the polarization rotation and hence the glucose concentration in the sample.

This is because for the foregoing 1 ampere value of AC modulation current and 0.02 milliampere value of DC balance point bias current, the slope of curve B in Fig. 3 at points B1 and B2 is sufficiently steep that only a small fraction of the noise superimposed on the AC modulation waveform affects the DC balance point. Stated differently, the projection of the noise component at points B1 and B2 on curve B of Fig. 3 onto the horizontal axis is very small and therefore does not produce an unacceptably large uncertainty or noise voltage on the value of the current applied to the coil of the Faraday rotator to obtain the DC balance point provided that the stability of the AC voltage amplitude is precise to about plus or minus 0.001 volt.

The DC current acts to balance the optical system so that at the positive and negative peaks an equal amount of light is passed. The light passed is converted to a voltage or current by detector 10, and is sent to a lock-in amplifier 45. The lock-in amplifier 45 is phase adjusted such that when Faraday rotator 20 is balanced the output of the lock-in amplifier 45 is zero. Any slight imbalance in the DC null position will yield a non-zero detection output signal.

The DC current corrects for steady-state imbalances in the

system and for the DC null point imbalance that is introduced by placing a sample in the optical path. Subtracting the current which is required to null the system at steady state with no sample from the current required to produce null with the sample

5   present gives the current change, or current delta (∆). It is this delta value which is then interpreted to represent a value of glucose concentration.

     The DC current source 31 is precisely adjustable from 0 to 500 milliamperes by setting a ten-turn potentiometer 80 (Fig.

10   5A). This sets a reference voltage that is converted to a current by a voltage-to-current amplifier circuit 30. Feedback is provided through a current sensing resistor 73. This samples the current and converts it back to a voltage which is then compared to the reference.

15   Precision and stability are attained by using a low DC drift operational amplifier 74, a good voltage reference FET 85, and the ten-turn potentiometer 80. The current sensing resistor is chosen to be a low enough value to avoid self heating effects, which would cause a shift in its resistance. However, the

20   resistor cannot be overly low in value, because the resulting low sensing voltage would cause offsets and drift in the operational amplifier 74 to become a problem. The ground point of the reference FET 85 must connect as directly as possible to the ground point of the current sensing resistor to avoid errors due

to resistance in ground lines.

Operational amplifier turn-on transients can cause an unacceptable current spike at the current source output. This is avoided by using a relay 68 which is energized directly from the power supply. The relay contacts engage after about a 10 millisecond delay, allowing the operational amplifier ample time to stabilize. The relay then connects the current source output to the load.

To allow complete independence from other signals, the current source is allowed to float with respect to the system ground. Consequently, this circuit has its own independent power supply 30.

Because the precision of the AC signal waveform is somewhat less critical (even though the waveform amplitude is critical), the AC circuit 35,36 has a voltage output for simplicity. An oscillator 35, set at about 475 Hz, drives a power amplifier 36. (Actually, an oscillator frequency between about 200 and 10,000 Hz would be acceptable.) The amplifier 36 is adjusted to provide about 15 volts peak-to-peak drive signal to Faraday rotator 20.

The filter circuitry 33,37 serves to allow the AC and DC components to combine, and prevents interaction between the AC and DC circuits. In the first filter section 33, DC current is

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blocked both to and from the output of AC amplifier 36 by a non-
polarized low-leakage capacitor in series with the amplifier
output. In the second filter section 37, AC feeding back toward
the DC current source is highly attenuated by a two pole L-C

5   (inductor-capacitor) network However, DC is allowed to pass from
the current source to the load without attenuation. The
capacitor in this section is also a low-leakage type and is non-
polarized.

       Light 55F is converted by a photodiode 10 which is sensitive

10   to light having a wavelength from about 400 to 1000 nanometers to
a small current. This current is then converted to a voltage
using a standard operational amplifier based photodiode
preamplifier circuit 48. The output of the photodiode
preamplifier 48 is sent to the signal input of a lock-in

15   amplifier 45. The output of oscillator 35 (at about 475 Hz) is
"shaped" by the circuit 38 shown in Fig. 5B to provide a clean
square wave and is sent to the reference input of the lock-in
amplifier 45. A digital meter 46 is used at the lock-in
amplifier output to provide a sensitive indication of the null

20   point (zero volts).

       The accuracy of this method relies on the capability of
determining the applied voltage/current and the precision with
which the null reading of the lock-in amplifier 45 can be
established. These two readings have been made to a precision

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that yields the null position to plus or minus 0.0001 degrees, which is clearly satisfactory for the determination of blood glucose levels in the clinically meaningful range.

An alternative method would be to insert two independent modulator/rotators into the optical path, one of them to be excited exclusively by the DC component of activation and the second to be excited solely by the required AC component. This approach could benefit the Faraday rotator methodology in that the AC/DC isolation filters would be replaced by a second coil/rotator element which might be less bulky than the filter components. (The PLZT modulator would not benefit from this implementation. That is, the PLZT device, being voltage driven rather than current driven like the Faraday rotator, would have a much simpler and more compact AC/DC isolation filter and thus would not benefit as much from the modification.)

Fig. 6 shows the precision of measurements of DC current applied to the activation coil of a Faraday rotator as a function of glucose concentration in a 1 centimeter path length cell when the above configuration was employed. The error bars on each data point are 0.002 millivolts and this value is approximately 2 times the line thickness as shown in the graph. Thus both sensitivity and precision are more than adequate for the measurements of sucrose concentrations over the desired range for a 1 centimeter path length.

Usual approaches to non-invasive optical measurements of

blood properties, principally oxygen concentrations (oximetry),

have concentrated on passing radiation through a finger or on

analyzing the reflected radiation. Preliminary analysis shows

that the path length through a finger, web of the hand, ear lobe,

cheek, tongue, etc. is adequate for the analysis of blood glucose

by polarization rotation even though the resultant path length is

only a few millimeters.

Such a measurement would be made in the near infrared (NIR)

region of the spectrum, which is the region where most organic

substances are basically transparent. This region is generally

accepted as being between about 700 nanometers and 2000

nanometers.

However, blood, being about 70% water, exhibits strong water

absorption characteristics. This absorption begins at a level of

about 0.01 cm^{-1} near 730 nanometers and rises to a level of 100

cm^{-1} near 1800 nanometers. Much "structure" in the curve of

absorption vs. wavelength exists between 1300 and 1800

nanometers, which will add to the complexity of extracting

glucose-related information from absorption measurements.

Another complication is the existence of blood-oxygen absorption

centered near 680 nanometers and extending to wavelengths of 750

nanometers. Thus the preferred measurement is with wavelengths

of about 780 nanometers through 850 nanometers.

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The passage of light through tissue is not purely a matter of accounting for optical absorption. Being an inhomogeneous medium, the tissue sample will scatter the radiation as well as absorbing it. This scattering is not quantifiable due to uncertainties in the exact nature of the tissue media.

However, it is known that such scattering will affect the polarization of the transmitted beam. The depolarization of optical beams due to small angle scattering is a well documented phenomenon. The shape of the scattering medium also can have a substantial effect on the depolarization parameters. For example, flat platelets (the shape of red blood cells) have a stronger depolarization effect than round particles. The net effect of such scattering depolarization is to produce a transmitted beam that is not truly linearly polarized, but rather is elliptically polarized. The effect of the elliptical polarization on the measurement in the absence of a quarter wave plate being incorporated into the system is that a true extinction, down to near zero amplitude, is not observed. Rather, as the analyzer is rotated through 180 degrees, one observes a maximum and a non-zero minimum of the detector output signal 11. The magnitude of the minimum of the detector output signal 11 is a measure of the amount of depolarization.

I have made measurements on the transmission through the finger tip including the nail bed, through the finger tip

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excluding the nail bed, and through the web of the hand between the thumb and the forefinger. Overall measurements at 785 nm indicate transmission levels of 10^{-3} to 10^{-4} with significant amounts of forward scattering. Utilizing these values together with an extinction ratio of 10^5 for the polarization spectrometer, it is clear that the true null position will result in a signal level that is well below even the theoretical noise level of room temperature detectors. The transmitted signal levels on the wings of the AC modulated system (refer to Fig. 3 and Fig. 4) are barely above the noise level of the detector system employed here, which is considerably above the theoretical noise level (undoubtedly by a factor of 10 or so). Since a signal to noise ratio of about 1000 is necessary in order to make accurate (5%) measurements in a reasonable time (less than 1 second) it will be necessary to increase the magnitude of the AC modulation drive to the modulator by about a factor of 10. For the case of the Faraday rotator this magnitude of drive current would result in unacceptably large heating of the coil. Thus, the only apparently feasible method of employing a Faraday rotator would be in a "burst" mode in which the coil is activated for a short (0.1 sec) time and then turned off for a longer time period (1 to 5 seconds). Simultaneously, even greater precision requirements are imposed on the stability and precision of the AC modulation voltage amplitude due to the much larger amplitude and its direct effect on the noise level of the DC measurement. A precision of at least one part per million is clearly required.

Thus, the alternative types of modulators (specifically the PLZT-based Kerr cell or the KDP based Pockels cell) are the preferred modulators for this situation since they are a very high impedance load presented to a voltage driver. This results in a very small power dissipation in the polarization modulator. The only remaining problem for these modulators is the stringent precision required of the driving voltage amplitude.

In all considerations it is assumed that careful attention is given to the frequency stability of the AC driving oscillator so that that source of noise is minimized for any case.

This technique of accounting for the scattering depolarization represents a critical component in assuring the successful analysis of blood glucose in vivo through the skin.

Note that the method does not require measurements at two or more wavelengths and thus does not suffer from problems associated with the interference of a varying background level of absorption which has presented such differential absorption approaches with major problems.

The ultimate size of the devices described herein can be quite small. A very small glass rod (2-4 millimeters diameter) can be employed as the active Faraday medium, which would result in a much smaller diameter activation coil. This coil would be

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wound with smaller diameter wire (#34-#40 gage) and thus could be driven at significantly lower currents. This would result in a very compact device having significantly reduced driving power. Alternatively, a very small Faraday rotator element can be produced by passing the light through an optical fiber which is enclosed by a small toroidal coil. By employing many windings of the fiber inside the toroid, the path length can be greatly increased and thereby compensating for the lower Verdet constant of the fiber's glass. Also a PLZT optical modulator can be made very small. Polarizers and wave plates can be fabricated in very small sizes. Thus, the entire device can be fabricated in a very small package, comparable for example to the size of a small pocket paging device.

By determining the sucrose levels in the aqueous humor, which has been proven to have a good quantifiable relationship to the blood sucrose concentration, it is possible to make the measurement in a simple and direct manner since there would be none of the above mentioned absorption and/or scattering effects which could complicate the measurement.

Fig. 7 shows a cross sectional diagram of the typical human eye 50 together with an indication of one optical path to be utilized for making glucose concentration determinations, as shown in Fig. 1 of the above King et al. article.

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In order to cause probing optical radiation 55A to sample the aqueous humor 53 in the anterior chamber of the eye, beam 55A,B,C passes transversely through the anterior chamber in the manner indicated in Fig. 7. Since the cornea/aqueous humor 54 is

5 an optical medium having an index of refraction of about 1.35, the incoming probe beam makes an angle of incidence on the cornea of about 70 degrees, as indicated in the diagram. In this case the parallel probe beam 55B passes through the anterior chamber approximately parallel to the iris, and thus no direct optical

10 radiation is directed into the eye and to the retina. (Any optical radiation which is scattered from optical defects of the cornea and from any floating particulates in the aqueous humor might produce some very small amount of radiation that reaches the retina of the eye through the pupil. This amount of

15 radiation will not be nearly sufficient to cause any retinal damage.)

During experimentation, I determined that there existed an alternate transverse path through the eye's anterior chamber 57. I found that this greatly reduced the experimental complexity of

20 making reliable measurements. This path is illustrated in Figs. 8A and 8B. In this preferred embodiment, the probing laser radiation 55A enters the anterior chamber 57 in a direction parallel to the eye's iris 56. That is, the probing radiation 55A is approximately parallel to the iris 56. The radiation is

25 refracted toward iris 56, and the optimum sensitivity of

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measurement is achieved when the laser spot is observed to strike the iris 56 at a point 58 very near the distal point of the iris. A simplistic ray trace of this path reveals that the radiation 55D reflected from point 58 is refracted again by the distal section of the cornea and, due to the symmetry of the cornea 54, it emerges as output beam 55C parallel to the input beam 55A and very nearly collinear with it, within a fraction of a millimeter. This means that the complete optical system can be easily aligned and optimized prior to the start of measurements on the eye.

Since the input beam to the eye and the output beam from the eye are collinear and only displaced from each other by a fraction of a millimeter or less, it is possible to simply align and calibrate the entire optical system without the presence of the eye and/or any other optical structure. This makes the system simple and straightforward to utilize. Note that if the path of Fig. 7 were to be employed, it would be necessary to zero or otherwise initialize the instrument with the eye or some surrogate optical elements in position since the input and output beams are significantly deviated from each other.

I have found that the experimental sensitivity from those subjects tested was nearly the same, within about 5%; this is probably because the human eye does not vary much in size from one individual to another,

When the laser beam 55A,B,C,D was transversing the eye's

anterior chamber 57, the frontal view of the eye with the visual

location of the laser reflection spot 58 on the iris had the

distinctive appearance shown in Fig. 8B. With this location of

5   the reflection spot 58, the largest portion of the total path

length through the anterior chamber 57 is on the incident, or

proximal, side of the point of reflection 58, with only a very

small portion 55D occurring following the reflection. This

factor is quite important, since the rotational direction of the

10   glucose in the anterior chamber following reflection is opposite

to that prior to reflection at point 58. Thus, the portion 55D

of the path length following the reflection will "unwind" or

cancel the polarization rotation which occurs during portion 55B

before reflection. For the above embodiment of the invention,

15   such "unwinding" is negligible. Incidentally, it has been

observed experimentally that no radiation is detected optically

by individuals in which the blood glucose measurements have been

made by this technique.

The spherical shape of the cornea and the location of the

20   iris 56 are such that the output beam 55C and the input beam 55A

of Figs. 8A and 8B are nearly collinear even though the position

of the input beam 55A may vary considerably during initial

positioning of the modified polarization spectrometer of the

present invention. This is apparently because the refracted beam

25   55B impinges on nearly the same point 58 of iris 56 for such

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different orientations.

Fig. 8C shows the output signal of detector 10 as the modified polarization spectrometer position is positioned so as to get a detection output signal. Numeral 92 indicates the detector output signal during the initial positioning of the polarization spectrometer, before input beam 55A is properly oriented. The portion of the signal indicated by numeral 92 consists of a several millivolt noise signal on the detection output. Numeral 93 indicates a slightly increased signal on the detection output as the input beam 55A is positioned so that the refracted beam 55B gets closer to a good reflection spot. Numeral 94 indicates a sudden increase in the detector output signal level from roughly zero volts to roughly 25 millivolts when the input beam 55A is positioned so as to produce the path shown in Fig. 8A, with the refracted beam 55B being reflected off of a spot on iris 56, producing the reflected beam 55D in the output beam 55C collinear with the input beam 55A.

I have found that if the subject simply holds still, the signal level indicated by numeral 95 remains steady (with several millivolts of noise superimposed thereon). Typically, 3 to 5 seconds of the signal level 95 is more than adequate for a precise adjustment of the DC balance point current applied to the Faraday rotator as needed to establish a precise value of the polarization rotation due to glucose in the anterior chamber of

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the eye.   Dotted line 96 indicates a return of the detector

output signal to essentially zero when the polarization

spectrometer device is then moved.   It should be noted that the

waveform shown in Fig. 8C indicates that there is no problem with

5   ambiguous or "false" output levels that can be mistakenly

misinterpreted.

This situation permitted a unique, simple and very effective

feedback method to be employed for assisting the subjects in

properly positioning their eyes for high quality measurement,

10   utilizing a branch prototype or model device.   The method

employed is illustrated by Fig. 9A which provides a description

of the apparatus employed in the human experiments.   The physical

setup includes a first turning mirror 69 which directs the laser

beam to a small (5mm x 5mm) 45 degree turning mirror 70 that

15   directs the beam to the eye's anterior chamber in the transverse

manner described above.   After transversing the eye's anterior

chamber 57, the output beam 55C is intercepted by a second small

45 degree turning mirror 71 which is located on the nasal side of

the eye.   This mirror redirects the light beam to the final large

20   turning mirror 72 which redirects the output beam 55C to the

final analyzer, focusing lens and silicon detector.   A camcorder

87 is positioned so that the viewing direction is within about 10

degrees of the normal to the eye and the camera is "zoomed in" so

that the subject's eye nearly fills the field of view.   The

25   camcorder (Sony Model TRV52 or equivalent) has an associated CCD

viewing screen 87A which can be deployed so that the subject can observe what the camera is recording, as indicated by dotted line 88.

During the measurement procedure, the subject focuses on the LCD viewing screen of the camcorder and can clearly observe the position of the laser spot 58 on his own iris. When the above scene diagramed in Fig. 8B is located, the subject then simply "freezes" that sight picture for the duration of the measurement, which is a few seconds. It was also found to be beneficial to the measurement stability if an image of the digital read out of the lock-in amplifier output signal as shown in Fig. 4 was superimposed onto one corner of the LCD viewing screen so that the subject could directly observe the results of the measurement.

Fig. 9B illustrates an embodiment of the invention similar to that of Fig. 9A except that fiber optic collimators 78, 79, 83, and 89 are used instead of the various turning mirrors.

The graph of Fig. 10 shows the experimental measurements of blood glucose concentrations made on two individuals by optical transmission through the anterior chamber of the eye by the method outlined above with reference to Figs. 8A,B and Fig. 9A. The data are accurate to about 5%.

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Figs. 11, 12, and 13 show proposed configurations of a miniaturized system based on the designs discussed above.

Fig. 11 shows a design for measurement "through the eye", and employs a miniature laser 2 with an output wavelength of 650 5 nanometers. Turning mirrors 91 and 92 are employed to route the laser light to and from the eye. The mirror separation is fixed. An electronics package (subsequently described) is configured to fit into available space inside the case. The package dimensions for this design are 3.0 inches wide X 3.75 inches long X 1.25 10 inches thick.

Fig. 12 shows a similar, generally equivalent design for measurement "through the eye", and employs a miniature laser 2 with an output wavelength of 650 nanometers. Fiber optic collimators are employed to route the laser light to and from the 15 eye. In this case the probe separation is fixed while the output collimator has a very small 45° turning mirror or prism 83A fastened to the end of a support member near the corner of the eye nearest the nose. The electronics package is configured to fit into available space inside the case, which is about 3.0 20 inches by 3.75 inches by 1.25 inches.

The polarizers, quarter wave plate, optical modulators, focusing lens, and detector in the embodiment of Fig. 12 can readily be obtained in very small sizes. All detection

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electronics, including the lock-in amplifier, can be included on one or two integrated circuit chips or in a single ceramic header. The modulator drive system can be fabricated on a small printed circuit board. Small, rechargeable batteries can be used. The overall package design size can be approximately 2.75" inches wide (+1.0 inches for the probe extensions) X 4.5 inch high X 1.5 inch thick.

Fig. 13 shows the design for a device for measurement "through the skin" and employs a miniature laser 2 with an output wavelength of 820 nanometers. Fiber optic collimators 74, 79, 82 and 83 are employed to route the laser radiation first to the input side of the measurement site and subsequently from the output side of the measurement site to the analyzer 7, focusing lens 9, and detector 10. The input/output (I/O) "probe" separation between fiber optic collimators 79 and 82 is adjustable as indicated by arrows 81 for the individual user by being mounted on a dovetail slide system 80 including stationary member 80B and slide member 80A while at the same time the optical components remain in alignment.

Referring again to Fig. 9A, the DC bias current and AC modulation current are applied to the coil of Faraday rotator 20 by Faraday rotator controller circuit 105, which includes the power supply 30, oscillator 35, current source 31, power amplifier 36, filter circuitry, lock-in amplifier 45, and

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detector/preamplifier circuit 48 of Fig. 5. Faraday rotator

controller circuit 105 is controlled via a bus 107 by a

microcomputer chip 106 which operates to automatically perform

the initial calibration of the device as shown in Figs. 11, 12,

5 and 13 by measuring a null in the detector output.

Microcomputer chip 106 also controls the previously

described nulling process during the portion 95 of the curve

shown in Fig. 8C, and also performs suitable averaging operations

to determine an accurate value of the DC shift in the current

10 applied to the coil of Faraday rotator 20 to establish a precise

DC null thereof after the anterior chamber of the eye or a

suitable tissue sample has been placed in the path of the beam.

Microcomputer chip 106 includes a clock and memory which

logs the time, date, and value of each successful glucose

15 concentration measurement by the patient, and effectuate

downloading of this information to another computer.

Microprocessor chip 106 also assists the patient in initially

aligning the hand-held device of Figs. 11 or 12 up to his or her

eye, align a red LED indicator reflected from the eye with a

20 suitable crosshair, indicates when low detection output signal

levels as indicated by numerals 92 or 93 in Fig. 8C have been

detected, illuminates a yellow LED when the signal level

indicated by numeral 95 has been detected to prompt the patient

to hold that position, and finally illuminates a green LED when

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the detector output signal level 95 has been maintained for the time period needed to accomplish the glucose concentration measurement.

The sensitivity of the above embodiments of the invention is demonstrably higher than that reported by Cote et al. in that I have successfully measured glucose levels in the eye's anterior chamber with a single pass rather than resorting to the multiple pass system described in their patent. Also, my approach depends on only a single detector/amplifier system, which is both simpler and lower in noise problems. In contrast to the above mentioned King et al. system, the AC and DC components of polarization rotation are carefully separated and can be treated as independent variables, which considerably reduces the instrumentational complexities and results in a greatly reduced noise level for the entire system. Since the variation of signal intensity near the null position varies as $\sin^2 \Delta\theta$ of the offset angle, any noise present in the AC modulation signal from the Pockels cell will show up in the null measurement sensitivity. The AC modulation to achieve nearly 9 degrees of polarization rotation must be compared to the measurement precision requirement of 0.0003 degrees. Thus a stability and noise filtering of the AC drive voltage of about 1 part in 100,000 must be addressed so that it does not constitute a serious noise problem. In the present invention the isolation of AC and DC components of modulator driving systems and attention to noise

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minimization in both the AC and DC components provides a
relatively noise free device and permits a measurement of DC
offset voltage to 1 part in 1,000,000 of the AC drive amplitude,
in contrast to the prior art.

5   Unlike the system described in the above mentioned Cote et
al. patent, my proposed device has no moving parts and thus is
free of any mechanically produced noise problems. My method of
employing a high quality quarter wave plate effectively results
in a significantly lowered noise level in that the null
10   extinction is of higher quality than that obtainable with the
instrumentation described in the above mentioned article by King
et al.

        While the invention has been described with reference to
several particular embodiments thereof, those skilled in the art
15   will be able to make the various modifications to the described
embodiments of the invention without departing from the true
spirit and scope of the invention. It is intended that all
combinations of elements and steps which perform substantially
the same function in substantially the same way to achieve the
20   same result are within the scope of the invention. For example,
it is possible that a film covering the cornea, or the cornea
itself, may include concentrations of glucose which could be
measured by ellipsometric techniques applying the principles of
the invention. Furthermore, optically active ingredients other

than glucose which effect polarization rotation of a beam in a
sample may be measured using the basic techniques of the present
invention. The sample may be other than a biological sample.
The relative positions of quarter wave plate and the analyzer and
the sample can be different than in the described embodiments.
The light does not have to be perfectly monochromatic.
Theoretically, the initial measurement could be made with the
sample in the light path, with the analyzer rotated relative to
the polarizer to extinguish the beam reaching the detector, the
sample removed, and the DC signal shift needed to again
extinguish the beam reaching the detector would represent the
glucose concentration in the sample.